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Fr m: Gabel, Gailene
Sent: Tuesday, July 30, 2002 5:18 PM
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Please provide a copy of the following references:

1) Nakamura et al., Serologic markers in inflammatory bowel disease, MLO: medical laboratory observer, November 2001, vol. 33 (11): 8-15.

2) Cohavy et al., Colonic bacteria express an ulcerative colitis pANCA-related protein epitope, Infection and Immunity, 2000 Vol. 68 (3): 1542-1548.

3) Oh et al. Optimization of four IBD serology markers for increased IBD diagnostic accuracy, Gastroentorology Vol. 120 (5 Supplement 1): pA274, April 2001.

4) Vermeire et al. Combining serologic antibodies ASCA and anti-OmPC increases sensitivity for Crohn's Disease (CD), Gastroentorology 120 (5 Supplement 1): pA274, April 2001.

Thanks a bunch!!!

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L1: Entry 1 of 2 File: USPT

DOCUMENT-IDENTIFIER: US 5830675 A
TITLE: Methods for selectively detecting perinuclear anti-neutrophil cytoplasmic antibody of ulcerative colitis, primary sclerosing cholangitis, or type 1 autoimmune hepatitis

Assistant Examiner (1):
Portner; Ginny Allen

Brief Summary Text (4):
Inflammatory Bowel Disease (IBD) is the collective term used to describe two gastrointestinal disorders, ulcerative colitis ("UC") and Crohn's disease ("CD"). IBD occurs world-wide and is reported to afflict as many as two million people. Onset has been documented at all ages; however, IBD predominately affects young adults.

Brief Summary Text (5):
The three most common presenting symptoms of IBD are diarrhea, abdominal pain, and fever. The diarrhea may range from mild to severe and is often accompanied by urgency and frequency. In UC, the diarrhea is usually bloody and may contain mucus and purulent matter as well. Anemia and weight loss are additional common signs of IBD.

Brief Summary Text (6):
A battery of laboratory, radiological, and endoscopic evaluations are combined to derive a diagnosis and to assess the extent and severity of the disease. Nevertheless, differentiating UC from CD, as well as other types of inflammatory conditions of the intestines, such as irritable bowel syndrome, infectious diarrhea, rectal bleeding, radiation colitis, and the like, is difficult. Indeed, depending on the period of follow-up time, in many patients the colitis must be regarded as indeterminate or cannot be definitively diagnosed because of the overlapping features of UC and CD, particularly with CD of the colon.

Brief Summary Text (7):
The selective identification of UC as opposed to CD or other inflammatory conditions of the intestines carries important prognostic and therapeutic implications. For example, when colectomy is indicated, the type of IBD involved determines which surgical options are appropriate. Surgery (total colectomy) does represent a cure in UC, though a dramatic one. In CD, surgery is never curative. Continent procedures such as the ileorectal pull-through (mucosal proctectomy) or the Kock pouch may be desirable in UC, but are contraindicated in CD.

Brief Summary Text (8):
The availability of a diagnostic marker that would readily distinguish UC from CD of the colon and other colitides would represent a major clinical advance. A convenient and reliable blood test which might parallel

disease activity or even predict an impending flare of activity would provide a tremendous advantage in the therapeutic management of IBD and aid in the design of more specific treatment modalities.

Brief Summary Text (9):
Although the cause(s) of UC and CD not known, there is general agreement that the immune system is responsible for mediating the tissue damage in these diseases. A wide range of immunologic abnormalities have been reported in these disorders, but none has yet been sufficiently reliable to be of diagnostic value.

Brief Summary Text (10):
A variety of autoantibodies has been observed in UC patients. Most notable among these antibodies have been lymphocytotoxic antibodies and colonic epithelial antibodies. Although these may have genetic and pathophysiologic implications, they have not been useful diagnostically either because of low frequency of occurrence or lack of specificity.

Brief Summary Text (11):
Two other inflammatory diseases which are also suspected of having autoimmune eitologies are primary sclerosing cholangitis ("PSC") and type 1 autoimmune hepatitis ("Type 1 AIH"). Like UC and CD, these liver diseases share common outward symptoms necessitating the use of invasive technologies, such as liver biopsy and/or ERCP to identify distinguishing liver abnormalities associated with AIH and PSC.

Brief Summary Text (12):
PSC is characterized by obliterative inflammatory fibrosis of the extrahepatic bile ducts with or without involvement of the intrahepatic ducts. The disease generally progresses in an unrelenting, albeit unpredictable, fashion to cirrhosis, portal hypertension, and death from liver failure. PSC can occur alone or in association with UC and less commonly with a variety of other diseases. Symptoms commonly include jaundice, puritis and nonspecific upper abdominal pain. Medical treatment of PSC has included corticosteroids, antibiotics, immunosuppressants, and cholecystogues alone or in combination. In general, results with all have been disappointing.

Brief Summary Text (15):
Accordingly, there has existed a need for a convenient and reliable method to distinguish UC from CD of the colon, and PSC from Type 1 AIH for diagnostic, prognostic and therapeutic purposes.

Brief Summary Text (17):
The present invention provides methods of detecting and measuring the presence or absence of perinuclear anti-neurtrophil cytoplasmic antibodies ("p-ANCA") of ulcerative colitis ("UC"), primary sclerosing cholangitis ("PSC") or type 1 autoimmune hepatitis ("Type 1 AIH") in a sample. More specifically, the presence of p-ANCA of UC, PSC or Type 1 AIH is detected by assaying for the loss of a positive value (i.e., loss of a detectable marker as compared to a control) upon treatment of neutrophils with DNAase. The present invention demonstrates that the p-ANCA associated with Type 1 AIH is different from that associated with PSC and that each of those p-ANCA are different than the p-ANCA related to UC. These differences can be relied upon to screen for each of the p-ANCA, the p-ANCA associated disease, and to differentiate between the three.

Brief Summary Text (19):
The present invention also provides kits containing reagents useful for identifying the presence or absence of p-ANCA of UC, PSC or AIH in a sample. The kits include, among other reagents, fixed neutrophil and a detectable secondary antibody.

Drawing Description Text (3):

FIG. 2 illustrates the staining patterns generated with UC patient serum previously characterized as containing p-ANCA. (A) p-ANCA staining pattern generated with p-ANCA positive UC serum on untreated neutrophil. (B) Staining pattern generated with p-ANCA positive UC serum on untreated neutrophil. (C) Abolition of p-ANCA staining pattern with p-ANCA positive UC serum after DNAase treatment of neutrophil- (D) Cytoplasmic (c-ANCA) homogeneous (or mushy) staining pattern with p-ANCA positive UC serum after DNAase treatment of neutrophil.

Drawing Description Text (4):
FIG. 3 illustrates the indirect immunofluorescent staining patterns generated with p-ANCA positive UC patient serum, anti-DNA serum and propidium iodide on methanol-fixed neutrophil (top row) and DNAase-treated, methanol-fixed neutrophil (bottom row). (A) Staining pattern generated with p-ANCA positive UC serum on methanol-fixed neutrophil, (B) Staining pattern generated with anti-DNA serum on methanol-fixed neutrophil. (C) Propidium iodide staining of methanol-fixed neutrophil. (D) Staining pattern generated with p-ANCA positive UC serum on DNAase-treated, methanol-fixed neutrophil. (E) Staining pattern generated with anti-DNA serum on DNAase-treated, methanol-fixed neutrophil. (F) Propidium iodide staining of DNAase-treated, methanol-fixed neutrophil.

Detailed Description Text (2):
The present invention provides methods and kits for detecting the presence of perinuclear anti-neutrophil cytoplasmic autoantibody (p-ANCA) for ulcerative colitis (UC), primary sclerosing cholangitis (PSC) or type 1 autoimmune hepatitis (Type 1 AIH) in a sample. Inventive methods involve assaying for the loss of a positive value (as compared to a control) upon treatment of neutrophils with DNAase. The inventive methods also involve the detecion of a particular staining pattern which can be correlated to the presence of a particular disease associated p-ANCA.

Detailed Description Text (3):
As the name indicates, antibodies to cytoplasmic components of the neutrophil are found in the serum of patients with certain chronic inflammatory conditions. By immunofluorescent microscopy, ANCA activity has been divided into two broad categories: cytoplasmic neutrophil staining (refered to herein as "c-ANCA staining pattern" or "cytoplasmic staining pattern") and cytoplasmic staining with perinuclear highlighting (refered to herein as "p-ANCA staining pattern" or "perinuclear staining pattern"). These distinct staining patterns are obtained with alcohol-fixed cytocentrifuged neutrophils. It has been reported that the p-ANCA staining pattern is an artifact of alcohol fixation which results when cytoplasmic granules re-locate to the periphery of the nucleus during the fixation process. However, the present invention provides evidence that the perinuclear staining pattern of p-ANCA associated with UC is not artifactual, but rather is the result of specific binding with a DNA associated antigen. Nevertheless, whether alcohol induced or actual, these staining patterns have served to distinguish between types of ANCA arising from unique antigens and having different disease associations.

Detailed Description Text (4):
The methods of the present invention exploit the unique staining patterns of UC, PSC and Type 1 AIH, as compared to one another, CD and other inflammatory conditions of the intestines, to provide a convenient and reliable method of identifying UC, PSC or Type 1 AIH, eliminating the uncertainty formerly associated with diagnosing and treating IBD and these liver diseases

Detailed Description Text (5):
One aspect of the present invention relates to methods of measuring the presence or absence of p-ANCA of UC or PSC in a sample, comprising: (a) contacting the sample and a detectable secondary antibody with immobilized neutrophils under conditions suitable to form a complex of neutrophil, p-ANCA and detectable secondary antibody, wherein said immobilized neutrophil is subjected to DNAase under conditions sufficient to

cause substantially complete digestion of cellular DNA without significant loss of nuclear or cellular morphology prior to said contacting step, and wherein said secondary antibody has specificity for p-ANCA or the class determining portion of p-ANCA; (b)separating unbound secondary antibody from the complex; (c) assaying for the presence or absence of p-ANCA containing complex by measuring the presence or absence of bound secondary antibody, compared to a control, wherein said control is the result of repeating the steps of the present method on a sample from the same source, except that the neutrophil of step (a) is not subjected to DNAase treatment.

Detailed Description Text (6):
In a related embodiment of the invention, the same method in an indirect immunofluorescence assay format can be used to detect the presence or absence of p-ANCA associated with Type I AIH, as well as the presence or absence of p-ANCA UC or PSC. Accordingly, there is provided a method of measuring the presence or absence of p-ANCA associated with UC, PSC, or Type 1 AIH in a sample, said method comprising: (a) contacting the sample and a detectable secondary antibody with fixed neutrophils under conditions suitable to form an immune complex of neutrophil, p-ANCA and detectable secondary antibody, wherein said fixed neutrophils are subjected to DNAase under conditions sufficient to cause substantially complete digestion of cellular DNA without significant loss of nuclear or cellular morphology prior to said contacting step, and wherein said secondary antibody has specificity for the class determining portion of p-ANCA; (b) separating unbound secondary antibody from the immune complex; (c)assaying for the pattern of p-ANCA immunoreactivity by detecting the presence, absence or pattern of complexed secondary antibody, compared to a control, wherein said control is the result of repeating the present method on a sample from the same source, except that the neutrophils are not subjected to DNAase.

Detailed Description Text (8):
In the methods of the present invention, neutrophils are subjected to DNAase under conditions sufficient to cause substantially complete digestion of cellular DNA. By the term "complete digestion of cellular DNA" it is meant such digestion of the cellular DNA that the cellular DNA has substantially lost its ability to bind proteins and other cellular materials normally associated with the cellular DNA of the neutrophil. Without being bound by any particular theory, it is presently believed that at least part of the antigens of p-ANCA of UC and PSC are proteins that are either intimately associated with nuclear DNA or with some aspects of nuclear structure.

Detailed Description Text (17):
Neutrophils and secondary antibody appropriate for use in the practice of the present invention will depend upon the origin of the sample assayed. As used herein, the terms "patient," "subject," or "individual" when referring to the origin of the sample to be assayed, means any animal capable of producing p-ANCA of UC, PSC or Type 1 AIH, including for example, humans, non-human primates, rabbits, rats, mice, and the like. Preferably, neutrophils and secondary antibody employed will have specific reactivity for the species from which the sample to be tested is obtained. For example, to assay for p-ANCA of UC, PSC, or Type I AIH in a sample obtained from a human subject, the neutrophils and the secondary antibody are preferably specific for humans. If multiple antibodies are employed, each antibody is preferably species-specific for its antigen.

Detailed Description Text (19):
The term "secondary antibody" as used herein, refers to any antibody or combination of antibodies or fragments thereof, at least one of which can bind p-ANCA of UC, PSC, or Type I AIH. For example, a secondary antibody can be an anti-p-ANCA antibody, specific for any epitope of p-ANCA, but preferably not one that would be competitive with neutrophil binding or cause steric hinderance of neutrophil/p-ANCA binding. Alternatively, a secondary antibody can be an anti-IgG preferably having specificity for the class determining portion of p-ANCA.

Detailed Description Text (22):
Preferably, the hybridomas are screened to identify those producing antibodies that are highly specific for the IgG of interest. The monoclonal antibody selected will have an affinity compatible with the desired sensitivity and range for detecting p-ANCA of UC or PSC. The use of such monoclonal antibodies provides a means of obtaining greater sensitivity in the assays of the present invention compared with the use of polyclonal antibodies.

Detailed Description Text (23):
Alternatively, monoclonal antibodies having a high affinity for p-ANCA of UC or PSC can be obtained by the creation of a phage combinatorial library for p-ANCA of UC or PSC and then screening for specificity by a similar process described in Barbas, C. F. et al, Proceedings of the Nat'l Academy of Science, 88:7978-82 (1991), incorporated herein by reference. The Examples below exemplify methods for making a phage combinatorialy library of an immunoglobulin gene repertoire for UC, as well as methods of screening the library for p-ANCA associated with UC. The nucleic acid and deduced amino acid sequence of the immunoglobulin heavy and light Fab chains of the two clones (5-3 and 5-4) of p-ANCA associated with UC are provided in SEQ ID NO:1 through 8. Anti-idiotypic antibodies to these and other clones of p-ANCA associated with UC can be raised by methods well known in the art. For example, polyclonal and monoclonal antibodies can be produced as described, for example, in Harlow and Lane, Antibodies: A Laboratory Manual (Cold Spring Harbor Laboratory 1988), which is incorporated herein by reference.

Detailed Description Text (25):
Monoclonal antibodies are typically composed of antibodies produced by clones of a single cell called a hybridoma that secretes (produces) but one kind of antibody molecule. In accordance with the present invention hybridomas capable of producing antibody material having specific immunoreactivity with p-ANCA associated with UC, but which does not prevent immunoreactivity of p-ANCA with neutrophil is provided. Such a hybridoma cell is formed by fusing an antibody-producing cell and a myeloma or other self-perpetuating cell line. The preparation of such hybridomas was first described by Kohler and Milstein, Nature, 256:495-497 (1975), which description is incorporated by reference. Polypeptide-induced hybridoma technology is also described by Niman et al., Proc. Natl. Sci., U.S.A., 80:4949-4953 (1983), which description is also incorporated herein by reference.

Detailed Description Text (26):
To obtain an antibody-producing cell for fusion with an immortalized cell, a mammal is inoculated with an immunogen. The word "immunogen" in its various grammatical forms is used herein to describe a composition containing a p-ANCA associated with UC as an active ingredient used for the preparation of the antibodies against p-ANCA associated with UC.

Detailed Description Text (27):
The amount of p-ANCA associated with UC used to inoculate the mammal should be sufficient to induce an immune response to the immunizing polypeptide. This amount depends, among other things, on the species of animal inoculated, the body weight of the animal and the chosen inoculation regimen as is well known in the art. Inocula typically contain about 10 micrograms of immunogen per inoculation for mice and may contain up to about 500 milligrams of immunogen per inoculation for larger mammals.

Detailed Description Text (28):
The spleen cells of the mammal immunized with p-ANCA associated with UC are then harvested and can be fused with myeloma cells using polyethylene glycol (PEG) 1500. Fused hybrids are selected by their sensitivity to HAT. Hybridomas producing an anti-p-ANCA idiotypic monoclonal antibody can be identified by screening hybridoma supernatants for the presence of antibody molecules that immunoreact with p-ANCA associated with UC. Such screening methods include for example, radioimmunoassay (RIA) or enzyme linked

immunosorbent assay (ELISA).

Detailed Description Text (30):
Another alternative for increasing the sensitivity of the assay of the present invention is to use a multiple antibody system for the secondary antibody, rather than using a single antibody with enhanced specificity. Thus, the methods of the present invention may be performed using a combination of antibodies as the secondary antibody, wherein at least one secondary antibody of the combination has specificity for p-ANCA or the class determining portion of p-ANCA and at least one secondary antibody of the combination is detectable. For example, UC and PSC may be distinguished from Crohn's disease in a sample of human blood by contacting two aliquots of blood serum from a patient with immobilized untreated or DNAase treated human neutrophil, followed by contacting the resulting antibody-antigen complex with mouse anti-human IgG. The resulting complex is then contacted with goat anti-mouse IgG having a detectable label and washed to remove unbound antibody. The resulting complex is assayed for the presence or absence of a detectable complex, compared to the control (i.e., non-DNAase treated neutrophil). The absence of the labeled goat anti-mouse IgG complexed with DNAase-treated neutrophils indicates that the patient has UC or PSC.

Detailed Description Text (31):
The term "detectible secondary antibody" refers to secondary antibody, as defined above, that can bind p-ANCA of UC or PSC and can be detected or measured by a variety of analytical methods. This term includes antibodies, or fragments thereof, that are directly detectible without attachment of signal generating labels, or those that can be labeled with a signal generating system to permit detection or measurement, such as, for example, any secondary antibody capable of being labeled with a radioisotope, enzyme, chromogenic or fluorogenic substance, a chemiluminescent marker, or the like. Alternatively, a secondary antibody can be made detectible by using biotin-avidin linkage to associate a label with the secondary antibody. In any of the above methods, the reactivity of the secondary antibody with the p-ANCA should not be significantly altered by the presence of the label. When a multi-antibody system is used as the secondary antibody, at least one of the antibodies, combination of antibodies or fragments thereof is capable of binding p-ANCA of UC or PSC, and at least one can readily be detected or measured by suitable analytical methods.

Detailed Description Text (39):
In accordance with the present invention, the presence or absence of p-ANCA of UC or PSC in the sample being tested is determined by contacting a sample with immobilized, DNAase treated neutrophils and secondary antibody, and assaying for the presence or absence of p-ANCA containing complex. The presence or absence of p-ANCA containing complex is determined by monitoring for the presence or absence of bound secondary antibody, compared to a control. P-ANCA is considered present in the test sample if there exists a loss of positive value (bound secondary antibody) in the test sample as compared to the control. The control is the result of repeating the same steps of the inventive method on a sample from the same source, when the immobilized neutrophil has not been subjected to DNAase.

Detailed Description Text (40):
For example, in an IIF assay format of the present methods the presence of p-ANCA of UC in a sample, and thus UC itself, is indicated when there is a loss of a perinuclear staining pattern, i.e., detectable complex associated with perinuclear staining pattern, as compared to said control. More preferably, the presence of p-ANCA of UC is further indicated by the absence of both a perinuclear staining pattern and a cytoplasmic staining pattern in the sample. Similarly, using the same IIF assay format the presence of p-ANCA of PSC in a sample, and thus PSC itself, is indicated when a homogeneous cytoplasmic staining pattern is detected in the sample and a perinuclear staining pattern is detected in the control, i.e., "conversion of detectable complex associated with perinuclear staining pattern to homogenous cytoplasmic staining pattern, as compared to said control." Likewise, using the same IIF assay format, the presence of p-ANCA of Type 1 AIH in a sample, and thus Type 1 AIH itself, is indicated when a granular cytoplasmic staining pattern is detected in the sample and

a perinuclear staining pattern is detected in the control, i.e., "conversion of detectable complex associated with perinuclear staining pattern to granular cytoplasmic staining pattern, as compared to said control." Finally, CD is indicated if the absence of a perinuclear staining pattern in the control is detected, i.e., "absence of a detectable complex associated with perinuclear staining pattern in said control."

Detailed Description Text (41):
In this manner, the methods of the present invention can be used to distinguish between p-ANCA of UC, p-ANCA of PSC and p-ANCA of Type 1 AIH, as well as to screen for any one of these p-ANCA, and thereby, preferably in combination with traditional diagnostic techniques, screen for any one of the diseases and distinguish them from CD.

Detailed Description Text (42):
For example, sera from 94 patients diagnosed with UC which were seropositive for p-ANCA, sera from ten patients diagnosed with PSC which were seropositive for p-ANCA, and sera from 22 patients diagnosed with Type I AIH which were seropositive for very high titre p-ANCA (mean ELISA value for neutrophil binding 139.+-.8) were analyzed for DNAase sensitivity in accordance with the methods of the present invention using a IIF assay format. As summarized in Table 1, loss of antigenic recognition after DNAase digestion of neutrophils demonstrated by the absence of any staining pattern is a dominant (66/94, 70%) characteristic of p-ANCA associated with UC.

Detailed Description Text (43):
On the other hand, the majority of p-ANCA associated with PSC and p-ANCA associated with Type 1 AIH p-ANCA recognize cytoplasmic components after DNAase treatment of neutrophils (7/10, 70% and 19/22, 86% respectively). When the patient sera is grouped based on whether the patient had UC or not (Table 2, UC/non-UC), it becomes clear that loss of perinuclear staining pattern after DNAase treatment of neutrophil is unique to p-ANCA of UC providing a reliable basis on which to screen for UC and differentiate p-ANCAs.

Detailed Description Text (48):
In yet another embodiment of the present invention there is provided, methods of differentiating p-ANCA of UC from p-ANCA of Type I AIH, and thus differentiating between the presence of the diseases, comprising: (a) contacting fixed neutrophils with a sample and a detectable secondary antibody under conditions suitable to form an immune complex of neutrophil, p-ANCA and detectable secondary antibody, wherein cellular DNA of the fixed neutrophils has been digested by DNAase without significant loss of nuclear or cellular morphology, and wherein the detectable secondary antibody is detectable by fluorescence and is specific for the class determining portion of p-ANCA; (b) separating unbound secondary antibody from the immune complex; and (c) detecting the immunofluorescent staining pattern of the complex as compared to a control, wherein the control is the result of repeating the present method using fixed neutrophils wherein the cellular DNA of the fixed neutrophils has not been digested by DNAase, and wherein the absence of a perinuclear staining pattern in the sample, and preferably the absence of a cytoplasmic staining pattern in the sample as well, and a perinuclear staining pattern in the control sample indicates UC, and wherein the presence of a granular cytoplasmic staining pattern in the sample and a perinuclear staining pattern in the control indicates Type I AIH.

Detailed Description Text (49):
In still another embodiment of the present invention there is provided methods of differentiating between p-ANCA of UC, p-ANCA of PSC, and p-ANCA of Type 1 AIH, and thus differentiating between the presence of the diseases, said method comprising: (a) contacting fixed neutrophils with a sample and a detectable secondary antibody under conditions suitable to form an immune complex of neutrophil, p-ANCA and detectable secondary antibody, wherein cellular DNA of the fixed neutrophils has been digested by DNAase without significant loss of nuclear or cellular morphology, and wherein the detectable secondary antibody is

detectable by fluorescence and is specific for the class determining portion of p-ANCA; (b) separating unbound secondary antibody from the immune complex; and (c) detecting the immunofluorescent staining pattern of the complex as compared to a control, wherein the control is the result of repeating the present method using fixed neutrophils wherein the cellular DNA of the fixed neutrophils has not been digested by DNAase, and wherein absence of a perinuclear staining pattern in the sample, and preferably the absence of a cytoplasmic staining pattern in the sample as well, and the presence of a perinuclear staining pattern in the control indicates UC; wherein the conversion of detectable complex associated with perinuclear staining pattern to homogenous cytoplasmic staining pattern, as compared to said control, indicates PSC; wherein conversion of detectable complex associated with perinuclear staining pattern to granular cytoplasmic staining pattern, as compared to said control, indicates Type I AIH; and wherein absence of a detectable complex associated with perinuclear staining pattern in said control indicates CD.

Detailed Description Text (50):
In another aspect of the present invention, kits for measuring the presence of the p-ANCA of UC, PSC, or Type 1 AIH in a sample are provided. A kit of the present invention can contain immobilized, DNAase-treated, alcohol fixed neutrophils and a detectable secondary antibody. Alternatively, a kit may contain immobilized neutrophils, DNAase and a detectable secondary antibody. Optionally, depending on the secondary antibody or label used, the kits may contain a signal generating substance to provide or enhance the detection of the p-ANCA of UC, PSC or Type 1 AIH. In addition, other components such as ancillary reagents may be included, for example, stabilizers, buffers, fixatives, such as methanol or ethanol, and the like. The reagents can be provided as dry powders, usually lyophilized, including excipients, which on dissolution will provide a reagent solution having the appropriate concentrations for performing the methods of the present invention.

Detailed Description Text (51):
A preferred embodiment of the inventive kit includes DNAase and human neutrophils immobilized on a solid substrate, preferably a microtiter plate or beads for detecting or quantitating fluorescence by a cell sorter. To detect the presence of p-ANCA of UC, PSC or Type 1 AIH, the kit preferably includes mouse anti-human IgG, and goat anti-mouse IgG labeled with an enzyme or a fluorogenic substance.

Detailed Description Text (52):
In yet another aspect of the present invention there is provided an isolated antigen of UC. The antigen naturally occurs in neutrophils and is characterized by its insolubility in Triton X-100.TM. which can be obtained from Fisher, Pittsburgh, Pa., catalogue number BP-151.

Detailed Description Text (95):
DNAase SENSITIVITY OF UC p-ANCA SPECIFIC ANTIGEN USING IMMUNOFLUORESCENCE ASSAY

Detailed Description Text (97):
Neutrophils treated with trypsin at various concentrations no longer reacted with UC p-ANCA positive sera nor with anti-histone positive serum, indicating that at least part of the p-ANCA reactive antigen is a protein. Similarly, pepsin digestion of neutrophils abolished PSC p-ANCA positive serum reaction, also indicating a proteinaceous character of that antigenic species. Panels of UC p-ANCA positive and c-ANCA positive patient sera were examined for DNAase sensitivity using cytocentrifuged, methanol-fixed slides as described above. Two other types of reactions were noted. Some p-ANCA positive sera lost the perinuclear aspect of the reaction and became cytoplasmic after DNAase treatment, while c-ANCA positive sera generally remained cytoplasmic. Additionally, some sera that were found to have both a perinuclear and cytoplasmic ANCA staining reaction always lost the perinuclear aspect of the reaction after DNAase treatment of neutrophils. These DNAase-induced staining patterns proved to be highly reproducible from experiment to experiment.

Detailed Description Text (99):

To determine whether DNAase treatment of neutrophils would abolish the antigenic recognition of all p-ANCA associated with UC, a panel (n=94) of UC patient sera, previously characterized as containing p-ANCA was examined for neutrophil binding after DNAase treatment using the IIF assay format. In 70% of the UC sera tested, DNAase treatment again resulted in the abolition of the immunogenic reaction that results in a p-ANCA staining pattern (FIG. 2A and C). The remaining p-ANCA positive UC sera were found to give a cytoplasmic (c-ANCA) homogeneous (or mushy) staining pattern after DNAase treatment of neutrophils (FIG. 2B and D). Thus, p-ANCA associated with UC yielded two possible reactions after DNAase treatment of neutrophils; 1) a p-ANCA reaction that is abolished and 2) a p-ANCA reaction that converts to a c-ANCA staining pattern. These changes in neutrophil staining patterns obtained after DNAase treatment of cells were a consistent feature of the sera tested and the same results were obtained in multiple experiments.

Detailed Description Text (102):
COMPARATIVE CHARACTERIZATION OF UC p-ANCA IMMUNOREACTIVE

Detailed Description Text (103):
To examine whether DNA integrity was necessary for UC p-ANCA binding to neutrophils, methanol-fixed neutrophils were treated with DNAase, contacted with p-ANCA positive serum from a patient diagnosed with UC, and UC specific p-ANCA binding examined by IIF. For comparative purposes the binding of a non-UC sera were also tested. Serum that expresses anti-DNA antibodies (Rheumatology Diagnostics Laboratories Inc., Los Angeles, Calif.), a serum that expressed WG ANCA, a serum that expresses anti-elastase antibodies, and that serum expresses antibodies to PR3 (the latter three all obtained from J. Charles Jennette University of North Carolina, Chapel Hill) were also contacted with DNAase treated, methanol-fixed neutrophils and binding examined by IIF. Additionally, the effectiveness of the DNAase digestion and subsequent loss of DNA was routinely monitored by staining neutrophils with the DNA binding dye, propidium iodide. FIG. 3 and 4 provide for comparison the IIF staining patterns generated with these serum with methonal-fixed neutrophil (top row) and DNAase-treated, methanol-fixed neutrophil (bottom row). As seen in FIG. 3A and D, the p-ANCA staining pattern generated by p-ANCA positive UC serum (FIG. 3A) is completely lost when neutrophil are pre-treated with DNAase (FIG. 3D) indicating that UC p-ANCA binding is abolished. A similar loss of antigen recognition after DNAase treatment was obtained, as expected, with the anti-DNA serum. FIG. 3B depicts the IIF staining pattern of anti-DNA serum on untreated neutrophils. This staining pattern is clearly lost when neutrophils are pre-treated with DNAase. (FIG. 3E) That DNAase treatment of neutrophils was effective in eliminating cellular DNA is seen in the lack of propidium iodide staining after such treatment (FIG. 3F) as compared to the propidium iodide staining pattern in the absence of DNAase treatment. (FIG. 3C) Neutrophil binding by WG serum was unchanged (FIG. 4A and D) by DNAase treatment of the cells while the anti-elastase p-ANCA staining pattern (FIG. 4B) was converted to a granular cytoplasmic pattern (FIG. 4E) by DNAase treatment. Finally, the staining pattern generated by anti-PR3 (FIG. 4C and F) was also unaffected by the DNAase digestion of neutrophils.

Detailed Description Text (106):
A panel of p-ANCA-containing sera from PSC and Type 1 AIH patients was examined and compared to the UC sera panel.

Detailed Description Text (128):
In a panel of p-ANCA positive UC sera, the subset found to lose greater than 50% of ANCA binding by ELISA corresponds to those that lost most or all of the p-ANCA staining by immunofluorescent staining. On the other hand, sera showing less than about 50% reduction in ANCA binding by ELISA were found to display a p-ANCA pattern that converted to cytoplasmic staining after DNAase digestion of neutrophils. In this latter group was also found a few sera with a mixture of perinuclear/cytoplasmic staining pattern that retained only the cytoplasmic pattern post DNAase treatment. The one serum displaying a cytoplasmic ANCA staining pattern was found to have increased ANCA binding post DNAase treatment. The majority (4 out of 6) of p-ANCA

positive PSC sera lost less than 50% of the ANCA binding after DNAase treatment of neutrophils; in contrast only 5 out of 14 UC p-ANCA positive sera showed such a loss. By immunofluorescent staining these PSC sera were found to display a p-ANCA staining pattern that became cytoplasmic after DNAase treatment.

Detailed Description Text (129):
Thus, the DNAase-treated, fixed neutrophil ELISA may be used to distinguish UC and PSC from CD, as well as other types of inflammatory conditions of the intestines. The unique perinuclear/cytoplasmic staining patterns associated with immunofluorescent-type assays confirms the reliability of ELISA assay and may allow further distinctions between UC and PSC.

Detailed Description Text (132):
In the pediatric population, distinguishing between UC, Crohn's disease (CD) and allergic colitis in children with rectal bleeding (RB) is particularly difficult. Since the occurrence of ANCA in adult patients with UC has been well established, studies were undertaken to determine the relationship between the occurrence of ANCA and pediatric UC. To determine whether the presence of ANCA, as measured by DNAase-treated fixed-neutrophil ELISA is sensitive and specific for pediatric UC, serum from children with UC (mean age=13), CD (mean age=14), RB (mean age=3) and other gastrointestinal inflammatory disorders (mean age=8) were tested in a blinded fashion. All ELISA positive samples were examined using immunofluorescence assay described above to determine ANCA staining patterns. ANCA was expressed as a percentage of UC positive sera binding and defined as positive when the value exceeded 2 standard deviations above the mean for normal control sera (.gtoreq.)12%. The results are presented in Table 3.

Detailed Description Text (133):
Seventy-two percent of children with UC were ANCA positive compared to 17% with CD, 23% with RB and 7% with other gastrointestinal inflammatory disorders (Table 1). The mean percent of positive control at 1:100 dilution was also significantly higher in UC ($p<0.00$ vs CD and non-IBD, $p<0.01$ vs RB). In addition, mean titers of ANCA positive samples were significantly higher, making ELISA titer very specific for UC. The presence of a perinuclear immunofluorescence pattern correlated with titer. It is therefore seen that ANCA is sensitive (72%) and specific (89%) for UC versus other inflammatory disorders.

Detailed Description Text (135):
ANTIGEN REACTIVE WITH p-ANCA OF UC AND PSC IS TRITON X-100.TM. INSOLUBLE

Detailed Description Text (139):
4. Add 0.05 ml of a 1:20 dilution of UC p-ANCA positive serum or PSC p-ANCA positive serum in phosphate buffered saline to slides. Add 0.05 ml phosphate buffered saline to clean slides as blanks. Incubate for 30 minutes to one hour at room temperature in sufficient humidity to minimize volume loss.

Detailed Description Text (141):
After Triton X-100.TM., neutrophil morphology was clearly lost with no evidence of a clear nuclear structure upon reaction with anti-DNA serum. However, cellular DNA was not lost during Triton X-100.TM. treatment. Both UC p-ANCA positive sera and PSC p-ANCA positive sera showed strong reactivity with fixed Triton X-100.TM. neutrophil extract. Based upon Triton X-100.TM. insolubility, an enriched fraction of UC and PSC p-ANCA antigens can be prepared to isolate the antigens.

Detailed Description Text (144):
V.sub.H - and V.sub.L -encoding DNA homolog libraries of the heavy and light chain gene repertoire of lamina propria lymphocytes (LPL) cells from humans diagnosed with UC and seropositive for p-ANCA in a fixed neutrophil ELISA were randomly combined, expressed and the resulting antibody material screened for ability to bind neutrophil using a phage display technique. The antibody material having immunoreactivity with

neutrophil were then screened for p-ANCA staining pattern and for loss of the p-ANCA staining pattern using DNAase-treated neutrophil as means of identifying p-ANCA associated with UC.

Detailed Description Text (146):
In a process called panning as described by Parmley et al., Gene, 74: 305-318 (1988), the phage expressing heterodimeric antibody material having anti-neutrophil immunoreactivity are enriched and isolated. The heterodimeric antibody material is then assayed for further the presence of p-ANCA associated with UC by alcohol-fixed indirect immunofluorescence ("the IIF assay") and for loss of a positive p-ANCA staining pattern in the IIF assay using DNAase-treated alcohol-fixed neutrophil.

Detailed Description Text (149):
Polynucleotide synthesis ("amplification") primers that hybridize to these conserved sequences and incorporate restriction sites into the DNA homolog produced, restriction sites that are suitable for operatively ligating the DNA homolog to a vector, were constructed. More specifically, the primers are designed so that the resulting DNA homologs produced can be inserted into an expression vector in reading frame with the upstream translatable DNA sequence at the region of the vector containing the directional ligation means. Amplification with the primers described herein is performed on cDNA templates produced from total RNA isolated from LPL of a human diagnosed with UC and seropositive for p-ANCA.

Detailed Description Text (197):
PREPARATION OF SOLUBLE RECOMBINANT ANTI-NEUTROPHIL ANTIBODY MATERIAL OF UC AND LIBRARY SCREENING

Detailed Description Text (208):
The 5-3 Fab was characterized using the assays described herein. Strong binding (approx. 0.1 micrograms/milliliter) to fixed neutrophil in an ELISA format. It is also notable that 5-3 p-ANCA Fab is avid compared to UC serum, since optimal binding occurred at 1% serum (or approx. 0.1 milligrams/milliliter total IgG). Estimating that approx. 1% hyperimmune serum is antigen-specific, then the level of native p-ANCA IgG is approx. 1 microgram/ml, or similar in range to binding by monovalent Fab.

Detailed Description Text (210):
The 5-3 p-ANCA Fab was also tested by alcohol-fixed neutrophil IIF assay for the p-ANCA staining pattern. Immunofluorescent detection of neutrophil staining by 5-3 p-ANCA Fab yielded the same p-ANCA staining pattern produced by conventional UC serum. When the immunoreactivity of 5-3 p-ANCA Fab was tested for DNAase sensitivity in accordance with EXAMPLE VI above, as with conventional p-ANCA seropositive UC serum, DNAase I treatment of neutrophil caused the complete loss of detectable p-ANCA staining pattern. In addition, confocal microscopy demonstrated that 5-3 p-ANCA Fab binds antigen located inside the nuclear envelop, a characteristic found in p-ANCA seropositive UC serum.

Detailed Description Paragraph Table (1):
TABLE 1 _____ Reactions of p-ANCA expressing sera with DNase treated neutrophils No Treatment Post DNAase Treatment Neutrophil Staining Pattern Disease n perinuclear None cANCA _____ UC 94 94/94 (100%) 66/94 (70%) 28/94 (30%) Type 1 AIH 22 22/22 (100%) 3/22 (14%) 19/22 (86%) PSC (w/o UC) 10 10/10 (100%) 3/10 (30%) 7/10 (70%) _____

Detailed Description Paragraph Table (2):
TABLE 2 _____ Comparison of p-ANCA of UC and group of p-ANCA associated with diseases other than UC. No Treatment Post DNAase Treatment Neutrophil Staining Pattern Disease n perinuclear None cANCA _____ UC 94 94/94

(100%) 66/94 (70%) 28/94 (30%) non-UC 32 32/32 (100%) 6/32 (19%) 26/32 (81%)

Detailed Description Paragraph Table (3):

TABLE 3 ANCA IN PEDIATRIC ULCERATIVE COLITIS

MEAN MEAN # #ANCA+ % Positive Cont. Reciprocal Titer Patients (%) Total ANCA+ Total ANCA+

UC 29 21 (72) 44 57 527 705 CD 41 7 (17) 8 16 61 114 RB 13 3 (23) 8 17 87 208 Non-IBD 94 7 (7) 6 21 63 229

UC = ulcerative colitis CD = Crohn's disease RB = rectal bleeding

Detailed Description Paragraph Table (4):

SEQUENCE LISTING (1) GENERAL INFORMATION: (iii) NUMBER OF SEQUENCES: 24 (2) INFORMATION FOR SEQ ID NO:1: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 699 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: double (D) TOPOLOGY: circular (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO (iv) ANTI-SENSE: NO (v) FRAGMENT TYPE: N-terminal (vi) ORIGINAL SOURCE: (A) ORGANISM: Homo sapiens (F) TISSUE TYPE: Gut-associated lymphoid (G) CELL TYPE: Lymphocyte (vii) IMMEDIATE SOURCE: (B) CLONE: 5-3 (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 1..699 (D) OTHER INFORMATION: /codon.sub.-- start= 1 /product= "Human Heavy Chain of IgG ANCA associated with UC" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 1..15 (D) OTHER INFORMATION: /product="N-Terminal Tag" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 16..96 (D) OTHER INFORMATION: /label=FR1 /note= ""FR1"refers to Framework Region 1" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 97..111 (D) OTHER INFORMATION: /label=CDR1 /note= ""CDR1"refers to Complimentarity Determining Region 1" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 112..153 (D) OTHER INFORMATION: /label=FR2 /note= ""FR2"refers to Framework Region 2" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 154..204 (D) OTHER INFORMATION: /label=CDR2 /note= ""CDR2"refers to Complimentarity Determining Region 2" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 205..300 (D) OTHER INFORMATION: /label=FR3 /note= ""FR3"refers to Framework Region 3" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 301..327 (D) OTHER INFORMATION: /label=CDR3 /note= ""CDR3"refers to Complimentarity Determining Region 3" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 328..360 (D) OTHER INFORMATION: /label=FR4 /note= ""FR4"refers to Framework Region 4" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 361..651 (D) OTHER INFORMATION: /label=CH1 /note= ""CH1"refers to Constant Segment 1 of the Heavy Chain" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 652..678 (D) OTHER INFORMATION: /label=Hinge /note= ""Hinge"refers to Partial Hinge Segment of the Heavy Chain" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 679..699 (D) OTHER INFORMATION: /label=Hex-HTAG /note= ""Hex-HTAG"refers to Hexahistidine Tag" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 16..651 (D) OTHER INFORMATION: /label=Fd /note= ""Fd"refers to the Fd of the Heavy Chain" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 16..300 (D) OTHER INFORMATION: /label=VHSEGMENT /note= ""VHSEGMENT"refers to Variable Segment of the Heavy Chain" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 301..315 (D) OTHER INFORMATION: /label=D /note= ""D"refers to Diversity Segment" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 316..360 (D) OTHER INFORMATION: /label=JH /note= ""JH"refers to Joining Segment of the Heavy Chain" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 16..360 (D) OTHER INFORMATION: /label=VHDOMAIN /note= ""VHDOMAIN"refers to Variable Domain of the Heavy Chain" (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GCCCAGGTGAAACTGCTCGAGCAGTCTGGGGGAGGCGTGGTCCAGCCT48

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GGGAAGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGG96

GlyLysSerLeuArgLeuSerCysAlaAlaSerGlyPheThrPheArg 202530

AACTATGGCATGCACTGGGTCCGGCAGGCTCCAGGCAAGGGGCTGGAG144

AsnTyrGlyMetHisTrpValArgGlnAlaProGlyLysGlyLeuGlu 354045
TGGGTGGCAGGTATTTCCTCTGATGGAAGAAAAAAAAAGTATGTAGAC192
TrpValAlaGlyIleSerSerAspGlyArgLysLysLysTyrValAsp 505560
TCCGTGAAGGGCCGATTCACCATCTCCAGAGACAAGTCCAAGAACACG240
SerValLysGlyArgPheThrIleSerArgAspLysSerLysAsnThr 65707580
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LeuTyrLeuGlnMetAsnSerLeuArgAlaGluAspThrAlaValTyr 859095
TACTGTGCGAAATTGTCCCGCGCGGGTGGTTTTGACATCTGGGGCCAA336
TyrCysAlaLysLeuSerArgAlaGlyGlyPheAspIleTrpGlyGln 100105110
GGGACAATGGTCACCGTCTCTTCAGCCTCCACCAAGGGCCCATCGGTC384
GlyThrMetValThrValSerSerAlaSerThrLysGlyProSerVal 115120125
TTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCC432
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LeuGlyCysLeuValLysAspTyrPheProGluProValThrValSer 145150155160
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TCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAG624
SerSerSerLeuGlyThrGlnThrTyrIleCysAsnValAsnHisLys 195200205
CCCAGCAACACCAAGGTGGACAAGAAAGCAGAGCCCAAATCTTGTGAC672
ProSerAsnThrLysValAspLysLysAlaGluProLysSerCysAsp 210215220 AAAACTAGTCACCACCACCACCACCAC699
LysThrSerHisHisHisHisHisHis 225230 (2) INFORMATION FOR SEQ ID NO:2: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 233 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
AlaGlnValLysLeuLeuGluGlnSerGlyGlyGlyValValGlnPro 151015
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AsnTyrGlyMetHisTrpValArgGlnAlaProGlyLysGlyLeuGlu 354045
TrpValAlaGlyIleSerSerAspGlyArgLysLysLysTyrValAsp 505560
SerValLysGlyArgPheThrIleSerArgAspLysSerLysAsnThr 65707580
LeuTyrLeuGlnMetAsnSerLeuArgAlaGluAspThrAlaValTyr 859095
TyrCysAlaLysLeuSerArgAlaGlyGlyPheAspIleTrpGlyGln 100105110
GlyThrMetValThrValSerSerAlaSerThrLysGlyProSerVal 115120125
PheProLeuAlaProSerSerLysSerThrSerGlyGlyThrAlaAla 130135140
LeuGlyCysLeuValLysAspTyrPheProGluProValThrValSer 145150155160
TrpAsnSerGlyAlaLeuThrSerGlyValHisThrPheProAlaVal 165170175
LeuGlnSerSerGlyLeuTyrSerLeuSerSerValValThrValPro 180185190
SerSerSerLeuGlyThrGlnThrTyrIleCysAsnValAsnHisLys 195200205
ProSerAsnThrLysValAspLysLysAlaGluProLysSerCysAsp 210215220 LysThrSerHisHisHisHisHisHis 225230 (2) INFORMATION FOR SEQ ID NO:3: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 732 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: double (D) TOPOLOGY: circular (ii) MOLECULE TYPE: cDNA (iii) HYPOTHETICAL: NO (iv) ANTI-SENSE: NO (v) FRAGMENT TYPE: N-terminal (vi) ORIGINAL SOURCE: (A) ORGANISM: Homo sapiens (F) TISSUE TYPE: Gut-associated lymphoid (G) CELL TYPE: Lymphocyte (vii) IMMEDIATE SOURCE: (B) CLONE: 5-4 (ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 1..732 (D) OTHER INFORMATION: /codon.sub.-- start= 1 /product= "Human Heavy Chain of IgG ANCA associated with UC" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 1..15 (D) OTHER INFORMATION: /product="N-Terminal Tag" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 16..93 (D) OTHER INFORMATION: /label=FR1 /note= ""FR1"refers to Framework Region 1" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 94..108 (D) OTHER INFORMATION: /label=CDR1 /note= ""CDR1"refers to

Complimentarity Determining Region 1" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 109..150 (D) OTHER INFORMATION: /label=FR2 /note= ""FR2"refers to Framework Region 2" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 151..201 (D) OTHER INFORMATION: /label=CDR2 /note= ""CDR2"refers to Complimentarity Determining Region 2" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA (B) LOCATION: 202..297 (D) OTHER INFORMATION: /label=FR3 /note= ""FR3"refers to Framework Region 3" (ix) FEATURE: (A) NAME/KEY: misc.sub.-- RNA

Other Reference Publication (20):
Farrant, J.M., et al., "HLA DR2 is a Susceptibility Marker for UC in British Patients Irrespective of ANCA Positivity." Immunol. Microbio. Inflamm. Disorders, A679 (1994).

Other Reference Publication (44):
Tahir, S.K., et al., "Nuclear Localization of UC Specific Perinuclear Antineutrophil Cytoplasmic Antibody (pANCA) Reactive Antigen." Immunol. Microbio. Inflamm. Disorders, A779 (1994).

Other Reference Publication (46):
Vidrich, A., et al., "IgG Subclass Distinguishes Between PSC and UC ANCA." AASLD, A1015 (1992).

CLAIMS:

14. A method of differentiating the conditions of ulcerative colitis without primary sclerosing cholangitis, primary sclerosing cholangitis with or without concomitant UC, Crohn's disease and type 1 autoimmune hepatitis, said method comprising:

Search in SWISS-PROT and TrEMBL for: ompc

SWISS-PROT Release 40.24 of 26-Jul-2002
TrEMBL Release 21.5 of 26-Jul-2002

- Number of sequences found in SWISS-PROT(6) and TrEMBL(15): **21**
- Note that the selected sequences can be saved to a file to be later retrieved; to do so, go to the bottom of this page.
- For more directed searches, you can use the Sequence Retrieval System SRS.

Search in SWISS-PROT: There are matches to 6 out of 111818 entries

OMPC_ECOLI (**P06996**)
Outer membrane protein C precursor (Porin ompC) (Outer membrane protein 1B). {GENE: OMPC OR MEOA OR PAR OR B2215} - Escherichia coli

OMPC_KLEPN (**Q48473**)
Outer membrane protein C precursor (Porin ompC) (Porin ompk36). {GENE: OMPC OR OMPK36} - Klebsiella pneumoniae

OMPC_NEIGO (**P09888**)
Outer membrane protein P.IIC precursor (Protein IIC). {GENE: PIIC} - Neisseria gonorrhoeae

OMPC_RAHAQ (**O33507**)
Outer membrane protein C (Porin ompC) (Fragment). {GENE: OMPC} - Rahnella aquatilis

OMPC_SALTY (**O52503**)
Outer membrane protein C precursor (Porin ompC). {GENE: OMPC OR STM2267 OR STY2493} - Salmonella typhimurium, Salmonella typhi

OMPC_SERMA (**Q54471**)
Outer membrane protein C precursor (Porin ompC). {GENE: OMPC} - Serratia marcescens

Search in TrEMBL: There are matches to 15 out of 670277 entries

Q52641
OmpC (Fragment) {GENE:OMPC} - Rahnella aquatilis

Q8RLH3
Outer membrane protein (Fragment) {GENE:OMPC} - Salmonella pullorum

Q8RLH4
Outer membrane protein (Fragment) {GENE:OMPC} - Salmonella dublin
Q8RLH5
Outer membrane protein (Fragment) {GENE:OMPC} - Salmonella gallinarum
Q8X731
Protein histidine kinase/phosphatase sensor for OmpR, modulates expression of ompF and ompC (Protein histidine kinase/phosphatase EnvZ) {GENE:ENVZ OR Z4759 OR ECS4246} - Escherichia coli O157:H7
Q8XE41
Outer membrane protein 1b (Ib,c) (Outer membrane protein C OmpC) {GENE:OMPC OR Z3473 OR ECS3104} - Escherichia coli O157:H7
Q8ZGR1
Outer membrane protein C, porin {GENE:OMPC OR YPO1222} - Yersinia pestis
Q8ZGS6
Outer membrane protein C2 {GENE:OMPC2 OR YPO1205} - Yersinia pestis
Q93K99
OmpC porin precursor {GENE:OMPC} - Enterobacter cloacae
Q93T24
OmpC-type porin {GENE:OMPK36} - Enterobacter aerogenes (Aerobacter aerogenes)
Q9K3E6
Outer membrane protein C precursor {GENE:OMPC} - Salmonella enterica subsp. enterica serovar Minnesota
Q9K597
Outer membrane porin C precursor {GENE:OMPC} - Escherichia coli
Q9NGR8
Mechanosensory transduction channel NOMPC {GENE:NOMPC OR CG11020} - Drosophila melanogaster (Fruit fly)
Q9RH85
Outer membrane protein OmpC {GENE:OMPC} - Escherichia coli O157:H7
Q9VMR4
NompC protein {GENE:NOMPC OR CG11020} - Drosophila melanogaster (Fruit fly)

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L2: Entry 17 of 107 File: USPT

DOCUMENT-IDENTIFIER: US 6362002 B1
TITLE: Characterization of individual polymer molecules based on monomer-interface interactions

Detailed Description Text (29):
Examples of bacterial pore-forming proteins which can be used in the invention include Gramicidin (e.g., Gramicidin A from Bacillus brevis; available from Fluka, Ronkonkoma, N.Y.); LamB (maltoporin), OmpF, OmpC, or PhoE from Escherichia coli, Shigella, and other Enterobacteriaceae, alpha-hemolysin (from S. aureus), Tsx, the F-pilus, lambda exonuclease, and mitochondrial porin (VDAC). This list is not intended to be limiting.

09/600,148
(312) 474 9578
Jeff Sharps

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L2: Entry 50 of 107 File: USPT

DOCUMENT-IDENTIFIER: US 5985285 A
TITLE: Vaccines for plague

CLAIMS:

33. A method according to claim 32 wherein the in-vivo inducible promoter is selected from HtrA, nir.beta., OmpR, OmpC, or PhoP.

44. A vaccine as claimed in claim 18 wherein the DNA is positioned in frame with an in-vivo inducible promoter selected from the group consisting of htrA, nirB, ompR, ompC and phoP.

Gabel, Gailene

To: STIC-ILL
Subject: 09/575,061

Please provide a copy of the following references:

1) Nakamura et al., Serologic markers in inflammatory bowel disease, MLO: medical laboratory observer, November 2001, vol. 33 (11): 8-15.

2) Cohavy et al., Colonic bacteria express an ulcerative colitis pANCA-related protein epitope, Infection and Immunity, 2000 Vol. 68 (3): 1542-1548.

3) Oh et al. Optimization of four IBD serology markers for increased IBD diagnostic accuracy, Gastroentorology Vol. 120 (5 Supplement 1): pA274, April 2001.

4) Vermeire et al. Combining serologic antibodies ASCA and anti-OmPC increases sensitivity for Crohn's Disease (CD), Gastroentorology 120 (5 Supplement 1): pA274, April 2001.

Thanks a bunch!!!

Gailene R. Gabel
7B15
305-0807

Serologic markers in inflammatory bowel disease (IBD).

Nakamura R M; Barry M
Prometheus Laboratories, San Diego, CA, USA.

MLO: medical laboratory observer (United States) Nov 2001, 33 (11) p8-15; quiz 16-9, ISSN 0580-7247 Journal Code: 0225602
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Subfile: Health Administration

Inflammatory bowel disease (IBD) is a generic term that refers to **Crohn** 's disease and ulcerative colitis. **Crohn** 's disease (CD) is a granulomatous enteritis which can involve the ileum, colon, and other parts of the intestinal tract. The serologic responses seen in **Crohn** 's disease include antibodies to Saccharomyces cerevisiae, mycobacteria, bacteroides, listeria and E. coli. Many of these organisms may be involved in the pathogenesis of the **Crohn** 's disease. Ulcerative colitis is characterized by inflammation of the mucosa and submucosa of the large intestine. The CD and UC are considered to be distinct forms of IBD; however, there is a subgroup of CD with a UC-like presentation. In recent years, several serologic markers have been found to be useful for the diagnosis and differentiation of CD and UC. These markers include the following antibodies (a) 2pANCA, (b) ASCA, (c) pancreatic antibody, and (d) **OmpC** antibody. The application of a panel of markers with the use of an algorithm can identify specific subtypes of IBD that have different clinical courses and progression of the diseases. The application of the serologic markers is useful for diagnosis and management of CD and UC patients.

Tags: Human
Descriptors: *Biological Markers; *Inflammatory Bowel Diseases--diagnosis --DI; Antibodies, Antineutrophil Cytoplasmic--blood--BL; Education, Continuing; Fluorescent Antibody Technique, Indirect; Inflammatory Bowel Diseases--classification--CL; Inflammatory Bowel Diseases--immunology--IM; United States
CAS Registry No.: 0 (Antibodies, Antineutrophil Cytoplasmic); 0 (Biological Markers)
Record Date Created: 20011127

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2/9/4 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08439032 Genuine Article#: 285UW Number of References: 56
Title: Colonic bacteria express an ulcerative colitis pANCA-related protein epitope
Author(s): Cohavy O; Bruckner D; Gordon LK; Misra R; Wei B; Eggena ME; Targan SR; Braun J (REPRINT)
Corporate Source: UNIV CALIF LOS ANGELES,DEPT PATHOL & LAB MED, CHS 13-222/LOS ANGELES//CA/90095 (REPRINT); UNIV CALIF LOS ANGELES,DEPT PATHOL & LAB MED/LOS ANGELES//CA/90095; UNIV CALIF LOS ANGELES,DEPT OPHTHALMOL/LOS ANGELES//CA/90095; UNIV CALIF LOS ANGELES,DEPT MED/LOS ANGELES//CA/90095; UNIV CALIF LOS ANGELES,INST MOL BIOL/LOS ANGELES//CA/90095; ARIZONA STATE UNIV,DEPT MICROBIOL/TEMPE//AZ/85287; CEDARS SINAI MED CTR,INFLAMMATORY BOWEL DIS RES CTR/LOS ANGELES//CA/90048
Journal: INFECTION AND IMMUNITY, 2000, V68, N3 (MAR), P1542-1548
ISSN: 0019-9567 Publication date: 20000300
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Geographic Location: USA
Subfile: CC LIFE--Current Contents, Life Sciences
Journal Subject Category: IMMUNOLOGY; INFECTIOUS DISEASES
Abstract: Bacteria are a suspected pathogenic factor in inflammatory bowel disease, but the identity of the relevant microbial species remains unresolved. The pANCA autoantibody is associated with most cases of ulcerative colitis (UC) and hence reflects an immune response associated with the disease process. This study addresses the hypothesis that pANCA identifies an antigen(s) expressed by bacteria resident in the human colonic mucosa. Libraries of colonic bacteria were generated using aerobic and anaerobic microbiologic culture conditions, and bacterial pools and clonal isolates were evaluated for cross-reactive antigens by immunoblot analysis using the pANCA monoclonal antibody Fab 5-3. Two major species of proteins immunoreactive to pANCA monoclonal antibodies were detected in bacteria from the anaerobic libraries. Colony isolates of the expressing bacteria were identified as Bacteroides caccae and Escherichia coli. Isolation and partial sequencing of the B. caccae antigen identified a 100-kDa protein without database homologous sequences. The E. coli protein was biochemically and genetically identified as the outer membrane porin **OmpC** . Enzyme-linked immunosorbent assay with human sera demonstrated elevated immunoglobulin G anti- **OmpC** in UC patients compared to healthy controls. These findings demonstrate that a pANCA monoclonal antibody detects a recurrent protein epitope expressed by colonic bacteria and implicates colonic bacterial proteins as a target of the disease-associated immune response.
Identifiers--KeyWord Plus(R): INFLAMMATORY BOWEL-DISEASE; ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES; HLA CLASS-II; ESCHERICHIA-COLI; GENETIC-HETEROGENEITY; **CROHNS** -DISEASE; T-CELLS; C3H/HEJBIR MICE; OUTER-MEMBRANE; P-ANCA
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Optimization of four IBD serology markers for increased IBD diagnostic accuracy.
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ISSN: 0016-5085
RECORD TYPE: Citation
LANGUAGE: English
DESCRIPTORS:
MAJOR CONCEPTS: Clinical Chemistry (Allied Medical Sciences); Clinical Immunology (Human Medicine, Medical Sciences); Gastroenterology (Human Medicine, Medical Sciences); Serology (Allied Medical Sciences)
BIOSYSTEMATIC NAMES: Enterobacteriaceae--Facultatively Anaerobic Gram-Negative Rods, Eubacteria, Bacteria, Microorganisms; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: E. coli {Escherichia coli} (Enterobacteriaceae); human (Hominidae)--patient
ORGANISMS: PARTS ETC: bowel--digestive system; colon--digestive system; serum--blood and lymphatics
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Bacteria; Chordates; Eubacteria; Humans; Mammals; Microorganisms; Primates; Vertebrates
DISEASES: CD { **Crohn** 's disease}--diagnosis, digestive system disease, epidemiology, immune system disease; IBD {inflammatory bowel disease}--diagnosis, digestive system disease, epidemiology, immune system disease; UC {ulcerative colitis}--diagnosis, digestive system disease, epidemiology
CHEMICALS & BIOCHEMICALS: ASCA antibody; IgA {immunoglobulin A}; IgG {immunoglobulin G}; **OmpC** antigen; anti- **OmpC** --diagnostic marker; pANCA antibody
MISCELLANEOUS TERMS: Meeting Abstract
CONCEPT CODES:
00520 General Biology-Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals
10006 Clinical Biochemistry; General Methods and Applications
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
14004 Digestive System-Physiology and Biochemistry
14006 Digestive System-Pathology
15002 Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies
15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
31000 Physiology and Biochemistry of Bacteria
34502 Immunology and Immunochemistry-General; Methods
34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
36002 Medical and Clinical Microbiology-Bacteriology
36504 Medical and Clinical Microbiology-Serodiagnosis
37054 Public Health: Epidemiology-Organic Diseases and Neoplasms
37056 Public Health: Epidemiology-Miscellaneous
BIOSYSTEMATIC CODES:
06702 Enterobacteriaceae (1992-)
86215 Hominidae

2/9/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13582216 BIOSIS NO.: 200200211037
Combining serologic antibodies ASCA and anti- OmpC **increases sensitivity for** Crohn **'s disease (CD).**
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LANGUAGE: English
DESCRIPTORS:
MAJOR CONCEPTS: Clinical Chemistry (Allied Medical Sciences); Clinical Immunology (Human Medicine, Medical Sciences); Gastroenterology (Human Medicine, Medical Sciences); Serology (Allied Medical Sciences)
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae)--adolescent, adult, aged, middle age, patient
ORGANISMS: PARTS ETC: T cell--blood and lymphatics, immune system; bowel --digestive system; colon--digestive system
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Chordates; Humans; Mammals; Primates; Vertebrates
DISEASES: **Crohn** 's disease--diagnosis, digestive system disease, immune system disease; inflammatory bowel disease--diagnosis, digestive system disease, immune system disease
CHEMICALS & BIOCHEMICALS: ASCA antibody--diagnostic marker; IgG { immunoglobulin G}; anti- **OmpC** --diagnostic marker
MISCELLANEOUS TERMS: Meeting Abstract
ALTERNATE INDEXING: **Crohn** Disease (MeSH); Inflammatory Bowel Diseases (MeSH
CONCEPT CODES:
00520 General Biology-Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals
02506 Cytology and Cytochemistry-Animal
02508 Cytology and Cytochemistry-Human
10006 Clinical Biochemistry; General Methods and Applications
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
14004 Digestive System-Physiology and Biochemistry
14006 Digestive System-Pathology
15002 Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies
15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
24500 Gerontology
25000 Pediatrics
34502 Immunology and Immunochemistry-General; Methods
34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
36504 Medical and Clinical Microbiology-Serodiagnosis
BIOSYSTEMATIC CODES:
86215 Hominidae

2/9/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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